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(57) Abstract

The present invention provides a method for the treatment of hemorrhagic shock comprising administering to a human being or other mammal a medicament comprising glycine in an amount which is effective for improving survival from hemorrhagic shock. Further provided are specific application forms comprising glycine.

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A NEW USE FOR GLYCINE

The present invention relates to the use of glycine to improve survival from hemorrhagic shock either prophylactically or acutely and to specific application forms of glycine.

Hemorrhagic shock is caused by a massive and rapid blood loss due to rupture of a major blood vessel after severe trauma. Multiple organ failure after severe trauma is still a major cause of death in intensive care unit patients. After successful resuscitation of hemorrhagic shock, patients are menaced by the consequences of a general ischemia/reperfusion injury leading to the systemic inflammatory response syndrome. This syndrome is characterized by relase of numerous humoral mediators and enhanced leukocyte-endothelial interactions that result in generalized inflammation. Among the agents which mediate the leukocyte-endothelial interactions are cytokines, such as interleukines, tumor necrosis factor (TNF), platelet activating factor, leukotrienes, prostaglandins, and a variety of acute phase proteins. The development of irreversibility following prolonged hemorrhagic shock has also been attributed to loss of cellular energy and it has furthermore been postulated that oxygen-free radicals play a role in the development of irreversible hemorrhagic shock. Due to the complexity of the shock process, no single pharmacologic therapy has been capable of completely reversing the shock state.

It has now surprisingly been found that glycine improves survival from hemorrhagic shock.

The present invention therefore provides the use of glycine in the preparation of a medicament for the treatment of hemorrhagic shock.

The present invention also provides a method for the treatment of hemorrhagic shock comprising administering to a human being or other mammal a medicament comprising glycine in an amount which is effective for improving survival from hemorrhagic shock.

Treatment includes both prophylactic and acute treatment depending on the circumstances. In case of a major emergency operation glycine may be administered preoperatively, i.e. prophylactically. Where the hemorrhagic shock is caused by severe trauma due to e.g. an accident glycine will be administered immediately either before or during reperfusion, i.e. acute treatment. Both for prophylactic and acute treatment parenteral administration of glycine is preferred. It is essential that glycine is added before and/or during reperfusion so that elevated plasma levels are present during reperfusion. By the term elevated plasma levels is meant levels of glycine which are higher than 0.3mM.

Glycine may be administered to the patient in an amount such that the concentration of that amino acid in the patients's plasma is elevated to between 0.4 and 2.0 mM, preferably from 0.5 to 1.5 mM. Whilst concentrations higher than this are anticipated, it is expected that significant improvement of the patient's status will be obtained if the concentration of glycine is increased, so that it lies in the range of from 0.6 to 1.2 mM.

According to the invention, glycine is conveniently employed in free amino acid form, in pharmaceutically acceptable salt form, or in form of mixtures thereof. Glycine is preferably used in free amino acid form. Suitable salts include e.g. mineral or organic acid salts of the amino residue, and alkali or organic salts of the carboxylic acid residue.

The medicament may be so formulated as to deliver to the patient from 1 to 60 g, preferably 2 to 20 g, particularly preferred from 2.5 to 10 g of glycine, in particular about 5 g of glycine, preferably in one dosage either prophylactically or acutely.

Furthermore, the present invention foresees specific application forms of glycine which are suitable for use in emergency treatment. These application forms are for example suitable to be included in emergency sets of e.g. medical doctors or paramedicals

trained for ambulances. They include syringes, ampullas and infusion solutions comprising glycine in sterile solution.

The present invention, therefore, provides an application form selected from a syringe, ampulla or infusion bag comprising 1 to 50 g, preferably 2 to 20 g, particularly preferred about 5 g of glycine in sterile solution. Preferably, the syringe or ampulla contains about 5 g of glycine in 20 ml of sterile solution. The infusion bag preferably contains about 5 g of glycine in 250 ml of sterile solution.

Further provided is a kit or package for use in the method of the invention, said kit or package including 1 to 50 g of glycine in powder form and 10 to 300 ml of sterile solution, together with instructions to use. Preferably, the kit or package includes 3 to 10 g of glycine in powder form and 15 to 300 ml of sterile solution, more preferred 4 to 8 g of glycine in powder form and 18 to 25 ml or 200 to 300 ml of sterile solution, particularly preferred about 5 g of glycine and about 20 ml of sterile solution or about 5 g of glycine and about 250 ml of sterile solution. A preferred kit or package includes 5 g of glycine powder contained in a syringe and 20 ml of sterile solution in a small ampulla, whereby the sterile solution is preferably 0.9% NaCl solution. Upon use the contents of the ampulla is drawn up into the syringe whereupon the glycine is dissolved e.g. by shaking the syringe.

Sterile solutions as referred to above include 1) crystalloids (electrolyte mixes), i.e. 0.9% NaCl solution, Ringer's solution, lactated Ringer's solution, any physiological solution similar to Ringer's solution with or without glucose; 2) colloids (synthetic or non-synthetic plasma expanders), i.e. starches (Dextran), gelatines (e.g. Gelofusine®), albumine solutions, plasma and similar solutions. Ringer's solution is a sterile solution, containing from 3.23 to 3.54g of sodium (equivalent to from 8.2 to 9.0g of sodium chloride), from 0.149 to 0.165 of potassium (equivalent to from 0.285 to 0.315g of potassium chloride), from 0.082 to 0.098g of calcium (equivalent to from 0.3 to 0.36g of calcium chloride, in the form of $CaCl_2 \cdot 2H_2O$), from 5.23 to 5.80g of chloride (as NaCl, KCl and $CaCl_2 \cdot 2H_2O$) and water in

sufficient quantity to give 1000 ml solution. Lactated Ringer's Injection solution is a sterile solution containing from 2.85g to 3.15g sodium, as chloride and lactate), from 0.141 to 0.173g of potassium (equivalent to from 0.27g to 0.33g of potassium chloride), from 0.049 to 0.060g calcium (equivalent to from 0.18g to 0.22g of $CaCl_2.2H_2O$), from 2.31g to 2.61g of lactate, from 3.68 to 4.08g of chloride (as NaCl, KCl and $CaCl_2 \cdot 2H_2O$) and water in sufficient quantity to give 1000 ml solution.

Utility of glycine in treating or preventing diseases and conditions as hereinabove specified may be demonstrated in in vitro and in animal tests, for example with the methods hereinafter described. Rats receive either a control or glycine-containing modified AIN diet. A standard model of withdrawing blood until blood pressure in the 30-40 mm mercury range is being used. After one hour of this shock , blood volume is being restored. In this model the gold standard is survival. Enzyme release (such as creatine kinase, AST and ALT) and histology in key tissues (liver, lung, gut, intestine and kidney) are measured at time points dictated from the survival study. To evaluate mechanisms, hypoxia is measured using the 2-nitroimidazole marker and free radicals are trapped as PBN adducts and detected by electron spin resonance. Furthermore blood pressure in rats fed control diets is being diminished for 30 min followed by an intravenous infusion of glycine for 30 min. before restoration of blood volume to mimic the clinical picture with accident victims and major surgery patients. Tumor necrosis factor is being monitored in serum in these studies.

The invention is further illustrated by the Examples which are not intended in any way to limit the scope of the claimed invention.

Examples

Example 1

Methods

Hemorrhagic Shock Model:

Female sprague-Dawley rats (240-300 g) are anesthetized with pentobarbital sodium (50 mg/g body weight, i.p.) and body temperature is detected using a tele-thermometer (YSI 423s) placed in the anus and maintained at 37°C by warming lamps. Blood pressure is monitored via a polyethylene tubing (PE-50) inserted into the right femoral artery using a LPA low pressure analyzer (Digi-Med). The left jugular vein is cannulated (PE-50) for administration of glycine, lactated Ringer's solution and maintaining anesthesia with pentobarbital whenever the corneal reflex reappears. The right carotid artery is cannulated with a polyethlyene tubing (PE 90), and shock is induced by withdrawing blood into a heparinized glass syringe to reduce mean arterial pressure to 30-35 mmHg within 5 min and maintained by further withdrawal of small amount of blood when necessary. The total bleeding volume is about 27 ml/kg body weight in all groups studied. After 60 minutes of hypotension, rats are resuscitated by transfusion of 60% of shed blood and lactated Ringer's solution of 2-fold of shed blood volume over 1 h. Prior to resuscitation, animals are randomly assigned to a control or a glycine-treated group. Glycine (11-90 mg/kg body weight) is dissolved in 0.5 ml normal saline and injected into the left jugular vein and an equal volume of normal saline is given to the controls. In some experiments, rats are fed a powdered diet containing 20% casein (control diet) or 5% glycine and 15% casein (the glycine diet) and given glycine (45 mg/kg) just prior to shock to investigate the effects of glycine pretreatment compared to glycine-treatment only at the end of shock. Arterial blood samples are collected for determination of hematocrit, creatine phosphokinase, transaminases and creatinine levels. Immediately following resuscitation, catheters are removed, the vessels are occluded, and the wound is closed. Animals are placed in a warming blanket until consciousness is apparent and observed for 72 h for survival.

Determination of Creatine Phosphokinase, Transaminases and Creatinine

Blood samples are collected before and at the end of shock, at the end of resuscitation and 18 h later. Plasma is obtained by centrifugation, stored at -80°C, and creatine phosphokinase, aspartate-aminotransferase, alanine-aminotransferase and creatinine levels are determined using commercially available kits from Sigma.

Detection of Free Radical Adducts

To assess free radical formation, the spin trapping reagent N-t-butyl-α-phenylnitrone (PBN) is dissolved in normal saline (0.1M, 0.1 mmoles/kg body weight) and injected slowly into the left jugular vein just prior to plebotomy. Thirty minutes later, 1 ml of arterial blood from glycine or control group is collected into 2 ml 0.1 M PBN solution, the samples are centrifuged, and the plasma/PBN supernatant is stored on dry ice until analysis. Supernatants are extracted with 2:1 (v/v) chloroform/ methanol, the chloroform layer dried under nitrogen, and the resulting pellet resuspended in chloroform. Free radical adducts are detected with a Bruker ESP 106 ESR spectrometer. Instrument conditions are as follows: 20-mW microwave power; 1.0-G modulation amplitude, and 80-G scan range. Spectral data are stored on an IBM compatible computer and are analyzed for ESR hyperfine coupling constants by computer simulation. The magnitude of the first line of the 6-line signal is measured at identical gains and expressed in arbitrary units (1 unit = 1 cm chart paper).

Histological Procedures

Eighteen hours after resuscitation, organs are perfused with Krebs-Henseleit buffer (pH 7.4) to remove blood and fixed with 1% paraformaldehyde. Fixed tissue is embedded in paraffin and processed for light microscopy. Sections are stained with hematoxylin and eosin.

Statistical Analysis

All groups are compared using Student's t-test, Fisher-Exact test or ANOVA plus Student-Newman-Keuls test as appropriate, and differences are considered significant at the $p<0.05$ level.

Results

Blood Pressure and Hematocrit

The basal values of mean arterial pressure (MAP) is about 130 mmHg, a value decreased to 30-35 mmHg in 5 min and maintained for 1 h. MAP is increased to about 90 mmHg within 5 min upon resuscitation and reaches a steady state. Glycine treatment does not significantly alter mean, diastolic pressure, indicating that glycine does not significantly affect cardiovascular functions.

Basal hematocrit level is about 52% in both control and glycine-treated groups. This value is decreased to 42% at the end of the shock period and restored to about 45% at the end of resuscitation. Hematocrit levels are similar in controls and the rats receiving glycine, reflecting that glycine does not alter blood volume redistribution status compared to controls.

Survival after Hemorrhagic Shock

The control animals which only receive normal saline have a survival rate of only 16% 72 h after shock. Injection of glycine increases survival in a dose dependent manner; 80% of animals receiving glycine of 45 mg/kg body weight survive 72 h after shock. Rats receiving a glycine-containing diet plus a dose of glycine (45 mg/kg, i.v.) prior to shock have a survival rate similar to rats receiving only one dose of glycine (45 mg/kg, i.v.) prior to resuscitation (data not shown), therefore, presence of glycine during reperfusion is critical for the protective effect.

Effects of Glycine on Creatine Phosphokinase, Transaminase and Creatinine

Multiple organ failure is the major event responsible for mortality occurring after shock. Creatinine phosphokinase, an enzyme released into the blood when myocardial and skeletal muscle cells are damaged, is not significantly altered during shock but slightly increased during resuscitation. This enzyme is further increased 23-fold compared to basal levels at 18 h after resuscitation. Glycine largely blocks creatine phosphokinase release after shock. Basal levels of aspartate-aminotransferase and

alanine-aminotransferase are around 45 and 20 U/L respectively, values not significantly changed during shock and resuscitation. However, AST increases 35-fold and ALT increases 33-fold 18 h after resuscitation, indicating liver injury. Glycine significantly minimizes release of transaminase after shock. Creatinine levels are elevated 2.4-fold 18 h after resuscitation, reflecting a decreased renal function; this effect is also prevented by glycine treatment.

Effects of Glycine on Pathological Changes after Shock

Lung, kidney, liver, heart and small intestine specimens were taken 18 hours after shock/resuscitation. Lung specimens taken from control rats receiving saline injection at the end of shock exhibit hemorrhage, edema, marked increased cellularity in interstitial tissue and massive infiltration of inflammatory cells. Glycine (45 mg/kg) significantly minimized these phatological changes. In the kidney from control rats, proximal tubular cell necrosis, tubular cast and infiltration of leukocytes in interstitial tissue occurred in the cortex. In the outer medullary area, extensive hemorrhage, tubular cast and cell necrosis were observed, these alterations were significantly reduced by glycine. In the control rats receiving saline, some liver specimens (2/4) revealed infiltration of leukocytes and cell necrosis in the pericentral regions, and other specimens had mild fatty infiltration. Glycine prevented cell necrosis and leukocyte infiltration caused by shock, but did not alter fatty infiltration. No over pathological changes were observed in the heart and small intestine.

Effects of Glycine on Free Radical Production during Shock

A six-line free radical signal is detected in the blood before and during shock. The spectrum is computer simulated as composites of 3 radical adducts. Species I has hyperfine coupling constants of a^N =15.11 G and a^H =3.33 G; such coupling constants are characteristic of a carbon-centered PBN radical adduct. Species II has hyperfine coupling constants of a^N = 15.29 and a^H =6-66 G; characteristic of a 2-hydroxymethyl carbon-centered PBN radical adduct. Species III reveals coupling constants of a^N =14.12 G and a^H =2.29 G, most likely an oxygen-centered radical adduct. These values are matched closely with values of three species obtained from blood of rats after liver

transplantation. Free radicals signals are minimal before shock, values increase 4-fold during shock. Glycine significantly minimizes free radical production during shock.

Example 2 Application Forms

a) 20 ml syringe ready-to-use (for bolus injection), containing 5 g of glycine disolved in sterile 0.9% NaCl solution (= ca. 25% concentration).

b) Small ampulla, containing 5 g glycine dissolved in 20 ml sterile 0.9% NaCl solution as a concentrate. This concentrate will be added to a volume replacing solution (i.e. Ringer's or plasma expander) in an emergency situation. 1 ampulla will tpyically be added to 250 ml volume replacing solution.

c) Infusion solution, comprising 5 g of glycine dissolved in 250 ml of basic Ringer.

d) Kit of parts, comprising 5 g of glycine powder in a 20 ml syringe and 20 ml of sterile 0.9% NaCl solution in a small ampulla, whereby upon use the contents of the ampulla is drawn up into the syringe and the glycine powder is dissolved by shaking the syringe.

Claims

1. Use of glycine in the manufacture of a medicament for the treatment of hemorrhagic shock.

2. The use of claim 1 wherein the treatment is either prophylactic or acute and provides for elevated glycine levels during reperfusion.

3. An application form selected from a syringe, an ampulla or an infusion bag comprising 1 to 50 g, preferably 2 to 20 g, particularly preferred about 5 g of glycine in sterile solution.

4. A kit or package for use in the method as defined in claim 1 or 2, said kit or package including 1 to 50 g of glycine in powder form and 10 to 300 ml of sterile solution, together with instructions to use.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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